

# PATENT SPECIFICATION

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## COMPLETE SPECIFICATION

### Process for the production of Substituted Pyrazolones

We, FARBENFABRIKEN BAYER AKTIEN-GESELLSCHAFT, a body corporate organised under the laws of Germany, of 22c Leverkusen-Bayerwerk, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

This invention is concerned with a process for the production of N,N-disubstituted-4-aminomethylene-pyrazolones-(5) and of 4-formyl pyrazolones-(5) with unsubstituted 2-positions and is further concerned with new N,N-disubstituted - 4 - amino - methylene - pyrazolones-(5) and new 4-formyl pyrazolones-(5).

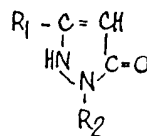
It is known to produce 4-formyl-pyrazolones-(5) with an unsubstituted 2-position by the reaction of 1,3-disubstituted pyrazolone-(5) derivatives either with phenyl isonitrile followed by hydrolysis of the so-obtained anile with alkali (M. Passerini and V. Casini, Gazz. chim. ital. 67, 332—36) or, using the Reimer-Tiemann reaction, with chloroform and saponifying with alkali the methenyl-bis-pyrazolone obtained with alkali (G. Losco, Gazz. chim. ital. 70, 284—86). Furthermore, aldehydes of the kind mentioned can be obtained according to M. Ridi (Gabb. chim. ital., 71, 542—48) by reacting 3- or 1,3-substituted pyrazolone-(5) derivatives with formamide. Methenyl-bis-pyrazolones are obtained which are hydrolysed in the above-described manner. According to M. Ridi, aldehydes of the type mentioned are also formed by reacting methenyl-bis-pyrazolones with formamide at 200° C. and hydrolysing with alkali, the 4-amino-methylene-pyrazolones formed under these conditions. According to M. Ridi, the 4-amino-methylene pyrazolones can be obtained by reacting the above-mentioned pyrazolones from the very beginning with a large excess of formamide. In this way, there first results the methenyl-bis-pyrazolones which, as already mentioned, react further with excess formamide to give the 4-aminoethylene-pyrazolones. Finally, a 4-amino methylene - pyrazolone - (5) derivative is obtained if, according to M. Ridi, 3-phenyl-

pyrazolone-(5)-aldehyde-(4) is reacted at 200° C. with formamide.

All these methods for the production of 4-formyl-pyrazolones-(5) with unsubstituted 2-positions and of 4-amino-methylene-pyrazolones-(5) are not very satisfactory and are not suitable for the technical production of these compounds either because difficultly obtainable starting products are used or the reaction only leads to these products under extreme conditions, such as a large excess of one component and high temperatures. Furthermore, in most cases it is a question of multi-step reactions which are also, to a greater or lesser degree, strongly influenced by side reactions.

It is further known to produce 4-formyl antipyrine by allowing methyl-phenyl-formamide or dimethylformamide to react on antipyrine in the presence of phosphorous oxychloride (I. Ito, J. pharm. Soc. Japan, 75, 167—169).

We have now found that 4-dialkylamino-methylene-pyrazolones-(5), 4-alkyl-aryl-amino-methylene-pyrazolones-(5), as well as 4-formyl-pyrazolones with unsubstituted 2-positions can be produced in a technically simple manner and usually with excellent yields by condensing pyrazolones of the general formula:—



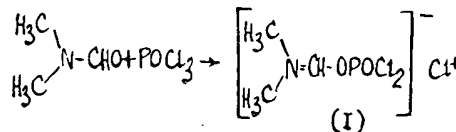
in which R<sub>1</sub> is a hydrogen atom or an alkyl, cyclo-alkyl, aralkyl or aryl residue, which can also be further substituted, (e.g. the 4-methoxyphenyl radical), a carboxyl group or a functional derivative thereof (e.g. the carbomethoxy radical) and R<sub>2</sub> is a hydrogen atom or an alkyl, cycloalkyl, aralkyl or a substituted or unsubstituted aryl radical (e.g. the *p*-tolyl radical), as well as a functional derivative of the carboxyl group or an amidinyl group, with N,N-dialkyl- or N-aryl-N-alkyl-formamides in the presence of chlorine-containing acidic condensation agents and in the presence or absence of solvents or diluting agents and the

so-obtained reaction mixture admixed with water, if desired with the addition of acid-binding agents to give an N,N-di-substituted-4-aminoethylene-pyrazolone-(5) which, if desired, may be further hydrolysed with water to give a 4-formyl-pyrazolone-(5).

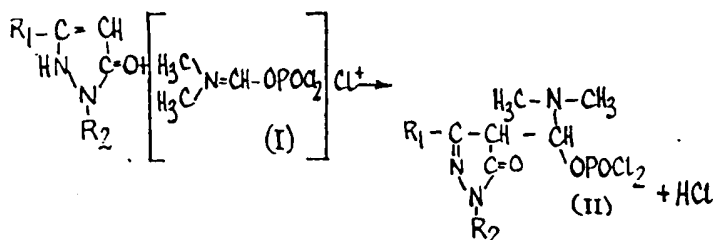
In this manner, the N,N-disubstituted-4-amino methylene-pyrazolone-(5) derivatives are exclusively, or preponderantly obtained, together with a small amount of aldehyde, if the decomposition of the reaction mixture is carried out at a temperature below room temperature and in neutral aqueous media. The 4-formyl-pyrazolones-(5) are obtained by hydrolysing the N,N-disubstituted 4-amino-methylene-pyrazolones-(5) in acidic media at an elevated temperature. It is to be under-

stood that is not, of course, necessary to isolate the N,N-disubstituted 4-amino-methylene-pyrazolones-(5) required for the production of the 4-formyl-pyrazolones-(5).

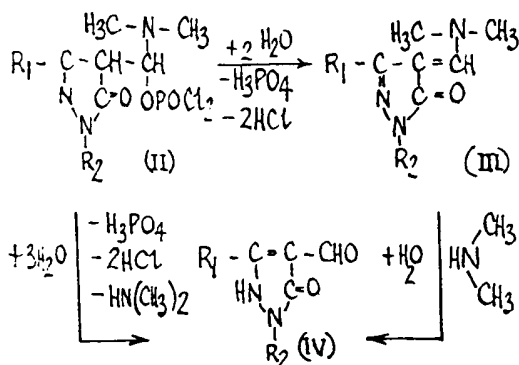
The reactions which take place may be exemplified as follows. By the reaction of dimethyl formamide with phosphorus oxychloride, an intermediate (I) is produced:



This intermediate (I) then reacts with a pyrazolone to give an intermediate (II):



The intermediate (II) can then be hydrolysed as follows:

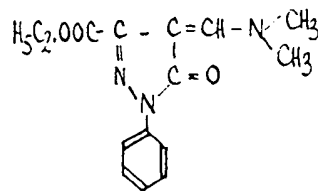


As will be appreciated from the above remarks, in order to obtain good yields of N,N-disubstituted 4-aminomethylene-pyrazolones-(5) it is necessary to use mild hydrolysis conditions for the decomposition of the intermediate (II). It will be appreciated that if more vigorous hydrolysis conditions are used, larger amounts of 4-formyl-pyrazolones-(5) will be formed.

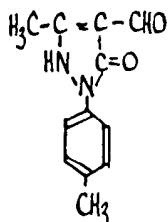
According to the results of the above-mentioned work by M. Ridi regarding the reaction of some pyrazolone derivatives of the above given general formula with formamide, a smooth and uniform course of this reaction was not to be foreseen since, in the case of the reaction of the components in the presence of condensation agents but otherwise under conditions such as are also used in the present process, almost quantitative amounts of methylene-bis-pyrazolones will result.

The new process differs substantially from the above-mentioned known reaction of antipyrine in that the pyrazolone derivatives of the above given general formula, in contradistinction to antipyrine, are also able fundamentally to react in the 2-position which is blocked by many acylation and alkylation reactions in the pyrazolone series. Thus, the close relationship may be pointed out of the basic reaction of the described process especially with acylation reactions. The differences between the two reactions can also be appreciated in that, in the case of antipyrine, N,N-disubstituted 4-amino methylene derivatives are not possible for structural reasons.

According to the invention, there is obtained, for example, the hitherto unknown 1-phenyl-3-carbethoxy-4-dimethyl-amino-methylene-pyrazolone-(5) of the formula:—



in that dimethyl formamide is allowed to react in the presence of phosphorus oxychloride with 1-phenyl-3-carbethoxy-pyrazolone-(5) and the so-obtained reaction mixture introduced at room temperature into a solution of sodium carbonate. 1-(p-Tolyl)-3-methyl-4-formyl-pyrazolone-(5) of the formula:—



may be obtained from the 1-(2-tolyl)-3-methyl-4-dimethylamino-methylene-pyrazolone-(5) by hydrolysis in an aqueous acidic medium at 70° C.

- 5 Other suitable pyrazolones of the above-given general formula are, for example pyrazolone-(5), 1-phenyl-3-methyl-pyrazolone-(5), 1 - (2<sup>1</sup> - chlorophenyl) - 3 - methylpyrazolone-(5), 1-(3<sup>1</sup>-chlorophenyl)-3-methylpyrazolone-(5), 1-(2<sup>1</sup>,5<sup>1</sup>-dichlorophenyl)-3-methylpyrazolone-(5), 1-(3<sup>1</sup>-nitrophenyl)-3-methylpyrazolone-(5), 1 - (4<sup>1</sup>-nitrophenyl)-3-methylpyrazolone-(5), 1-(3<sup>1</sup>-carboxyphenyl)-3-methylpyrazolone-(5), 1-amidino-3-methyl-pyrazolone-(5), 1,3-diphenyl-pyrazolone-(5), 1-phenyl-3 - (4<sup>1</sup> - methoxyphenyl) - pyrazolone - (5), 1-phenyl-pyrazolone-(5) carboxylic acid-(3), 1-phenyl-pyrazolone-(5)-carboxylic acid ethyl ester-(3), 1-phenyl-pyrazolone-(5)-carboxylic acid dimethylamide-(3) and 1-phenyl-pyrazolone-(5)-carboxylic acid diethylamide-(3).

- 15 Suitable formamides of the type mentioned are, for example, dimethyl formamide, diethyl formamide, dibutyl formamide and N-methyl-N-phenyl formamide.

- 25 As chlorine-containing acid condensation agents there can be used, for example, phosphorus oxychloride or phosgene.

- 30 Suitable solvents and dilution agents are those compounds which are inert under the reaction conditions and permit the solution of the reaction components in sufficient amounts, for example, aromatic hydrocarbons, such as benzene, and chlorinated aromatic hydrocarbons, such as chlorobenzene and *o*-dichlorobenzene.

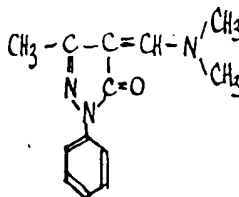
- 35 In general, the condensation is advantageously carried out in the temperature range of about 10—130° C.

- 40 Not only the 4-formyl-pyrazolones-(5) but also the N,N-disubstituted 4-aminomethylene-pyrazolones, as well as mixtures thereof, are important starting materials for the production of pharmaceutical products.

- 45 The following Examples are given for the purpose of illustrating the present invention parts by weight being related to parts by volume as grams to millilitres:—

#### 50 EXAMPLE 1

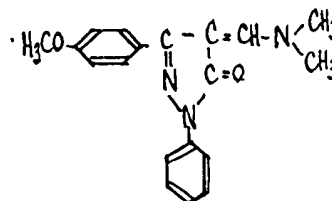
Production of 1 - phenyl - 3 - methyl - 4-dimethylaminoethylene-pyrazolone-(5).



55 507 parts by weight of phosphorous oxychloride are slowly added with stirring and cooling to 420 parts by weight dimethyl formamide at 5—15° C. After cessation of the generation of heat, 522 parts by weight of 1-phenyl-3-methylpyrazolone-(5) are slowly introduced into the so-obtained mixture. The temperature is then allowed to increase slowly from 15—70° C. A clear solution is obtained which is further stirred for 60 minutes at 70° C. and for 45 minutes at 80° C. The viscous reaction mixture is then allowed to flow, with stirring, into a mixture of 1260 parts by weight sodium bicarbonate in 4,000 parts by volume of water. If necessary, ice is added in order to ensure that the temperature does not exceed 30° C. Stirring is continued for a further 30 minutes at 35° C., the reaction mixture filtered off with suction, the residue washed with water and dried. An almost colourless powder is obtained. Yield: 595 parts by weight. Melting point: 127—132° C. The product is substantially pure and can be further used for most purposes in this form.

#### EXAMPLE 2

80 Production of 1-phenyl-3-(4<sup>1</sup>-methoxyphenyl) - 4 - dimethyl - aminomethylene) - pyrazolone-(5)

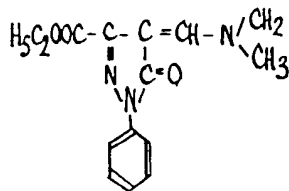


85 17.5 parts by weight dimethyl formamide and 20.2 parts by weight phosphorous oxychloride are mixed together in the manner described in Example 1. 32.0 parts by weight 1-phenyl-3-(4<sup>1</sup>-methoxyphenyl)-pyrazolone-(5) are introduced in small amounts, with stirring, into the so-obtained reactive mixture. The temperature thereby increases rapidly to 70° C. It is maintained by cooling at this temperature until the termination of the addition. The reaction mixture is subsequently slowly heated to 120° C. and stirring continued for 60 minutes at this temperature. The reaction mixture is then allowed to cool to 90° C. and the viscous reaction mixture poured into 1,500 parts by volume cold water, the simultaneous addition

of an aqueous solution of sodium hydroxide being made in order to ensure that the bulk of the liberated acid is neutralised. If necessary, the temperature, maintained below about 25° C. by the addition of ice. Stirring is continued for about 10 minutes, the reaction mixture filtered off with suction and the residue washed with water and dried. An almost colourless powder is obtained. Yield: 33.7 parts by weight. Melting point: 155–162° C. and, after recrystallisation from benzene-methyl cyclohexane, 164–166.5° C.

#### EXAMPLE 3

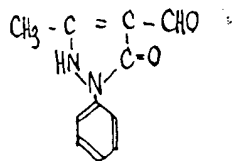
Production of 1-phenyl-3-carbethoxy-4-dimethylamino-methylene-pyrazolone-(5)



84.5 parts by weight phosphorus oxychloride are added dropwise with stirring at 10–15° C. to 65 parts by weight dimethyl formamide. 116.0 parts by weight 1-phenyl-3-carbethoxy-pyrazolone-(5) are added in small amounts with stirring to this mixture. The temperature thereby rises rapidly to 70° C. and is maintained at this level until the generation of heat ceases. Stirring is continued for a further 60 minutes at 70° C. and 60 minutes at 80° C. and the viscous reaction mixture then allowed to run slowly into 2,000 parts by volume cold water. The bulk of the acid which is thus liberated is neutralised by the simultaneous addition of sodium carbonate. The temperature is maintained at 15–20° C. by the addition of ice. Stirring is continued for a short period of time, the reaction mixture filtered off with suction and the residue washed with water and dried. An almost colourless powder is obtained. Yield: 129.7 parts by weight. Melting point: 114–120° C. and after recrystallisation from methyl cyclohexane 125–126° C.

#### EXAMPLE 4

Production of 1-phenyl-3-methyl-4-formyl-pyrazolone-(5)

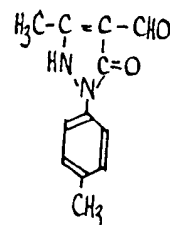


87 parts by weight 1-phenyl-3-methyl-pyrazolone-(5) are added portionwise with stirring to a reactive mixture obtained from 73 parts by weight dimethyl formamide and 84 parts by weight phosphorus oxychloride, prepared in the manner described in Example 1, the

temperature slowly rising to 70° C. Stirring is continued for 60 minutes at 60° C. and 45 minutes at 80° C. and the viscous solution then poured with stirring, into 1500 parts by volume water at 70° C., the mixture allowed to cool, while stirring, and filtered with suction. The residue is washed with water and dried. A yellow powder is obtained. Yield: 82 parts by weight. Melting point: 158–168° C. and after recrystallisation from benzene-methyl cyclohexane 171–172° C.

#### EXAMPLE 5

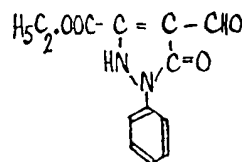
Production of 1-(4-tolyl)-3-methyl-4-formyl-pyrazolone-(5)



62 parts by weight dimethyl formamide and 84 parts by weight phosphorus oxychloride are mixed together in the manner described in Example 1. 94 parts by weight 1-(4-tolyl)-3-methyl-pyrazolone-(5) are added portionwise with stirring to this mixture, the temperature thereby rising slowly to 60° C. Shortly after the addition, the reaction mixture solidifies with a rapid increase of temperature to about 120° C. After cooling the bright, solid reaction product is added portionwise to 2,000 parts by volume water at 70° C. Stirring is continued for 15 minutes at 70° C., the mixture cooled to room temperature, filtered with suction and the residue washed with water and dried. A pale yellow powder is obtained. Yield: 101 parts by weight. Melting point: 160–172° C. and after recrystallisation from dioxane 173–174° C.

#### EXAMPLE 6

Production of 1-phenyl-3-carbethoxy-4-formyl-pyrazolone-(5)

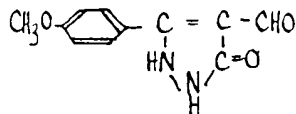


84.5 parts by weight phosphorus oxychloride are added dropwise, with stirring, to 73.0 parts by weight dimethyl formamide at 10–15° C. 116.0 parts by weight 1-phenyl-3-carbethoxy-pyrazolone-(5) are added in small amounts to this mixture with further stirring. The temperature thereby rises rapidly to 70° C. and is maintained at this level by cooling until the generation of heat has ceased. Stirring is continued for 60 minutes at 70° C. and 60

minutes at 80° C. and then the viscous reaction mixture is allowed to flow, with stirring, into 2,000 parts by volume water at 70° C. Stirring is continued for 15 minutes, the mixture  
 5 filtered with suction, the residue washed with water and dried. Yield: 128.1 parts by weight. Melting point after recrystallisation from benzene: 122—123° C.

## EXAMPLE 7

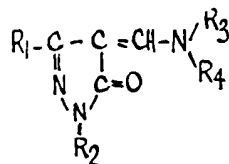
- 10 Production of 3-(*p*-methoxyphenyl)-4-formyl-pyrazolone-(5)



- In the course of about 40 minutes, 22.8 parts by weight 3-(*p*-methoxyphenyl)-pyrazolone-(5)  
 15 are added portionwise, with stirring, to a mixture of 35 parts by weight dimethyl formamide and 20.2 parts by weight phosphorus oxychloride heated to 80° C. The temperature is thereby allowed to increase to 120° C.  
 20 Stirring is continued for 30 minutes at 120° C. and the reaction mixture then introduced into 1500 parts by volume water at 55° C. Stirring is continued for a further 12 hours, the mixture filtered with suction, the residue washed with  
 25 water and dried. Yield: 23.7 parts by weight. Melting point after recrystallisation from glacial acetic acid: 258—262° C.

## WHAT WE CLAIM IS:—

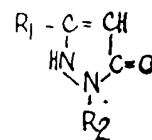
1. *N,N*-disubstituted-4-amino-methylene-pyrazolones-(5) of the general formula:—  
 30



- in which  $\text{R}_1$  is a hydrogen atom or an alkyl, cycloalkyl, aralkyl or aryl radical, which may be substituted, or a carboxyl group or a functional derivative thereof and  $\text{R}_2$  is a hydrogen  
 35 atom or an alkyl, cycloalkyl, aralkyl or a substituted or unsubstituted aryl radical, an amidinyl radical or a functional derivative of a carboxyl group,  $\text{R}_3$  is an alkyl or aryl radical and  $\text{R}_4$  is an alkyl radical.

2. 1 - phenyl - 3 - methyl - 4 - methyl-aminomethylene-pyrazolone-(5).  
 3. 1 - phenyl - 3 - (4-methoxyphenyl) - 4 - (dimethylamino-methylene)-pyrazolone-(5).  
 45 4. 1 - phenyl - 3 - carbethoxy - 4 - dimethylaminomethylene-pyrazolone-(5).

5. Process for the production of compounds of the general formula given in claim 1, wherein a pyrazolone of the general formula:—



in which  $\text{R}_1$  and  $\text{R}_2$  have the same significance as above, is condensed with an *N,N*-dialkyl- or an *N*-aryl-*N*-alkyl-formamide in the presence of a chlorine-containing acidic condensation agent and the reaction mixture obtained  
 55 decomposed in a neutral aqueous medium, optionally with the addition of an acid-binding agent at a temperature below room temperature to give an *N,N*-disubstituted-4-amino-methylene-pyrazolone-(5).  
 60

6. Process according to claim 5, wherein the reaction is carried out in the presence of a solvent or diluting agent.

7. Process according to claim 6, wherein the solvent or diluting agent is an aromatic or chlorinated aromatic hydrocarbon.  
 65

8. Process according to any of claims 5—7, wherein the condensation is carried out within the range of 10—130° C.

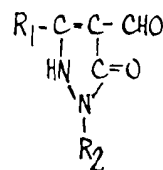
9. Process according to any of claims 5—8, wherein the chlorine-containing acidic condensation agent is phosgene or phosphorus oxychloride.  
 70

10. Process for the production of *N,N*-disubstituted-4-aminomethylene-pyrazolones-(5) of the general formulae given in claim 1, substantially as hereinbefore described.  
 75

11. Process for the production of *N,N*-disubstituted - 4 - aminomethylene - pyrazolones-(5) of the general formulae given in claim 1, substantially as described in any of Examples 1—3.

12. *N,N*-disubstituted-4-aminomethylene-pyrazolones-(5) of the general formulae given in claim 1, whenever prepared by the process according to any of claims 5—11.  
 85

13. Process for the production of 4-formyl-pyrazolones-(5) of the general formula:—



in which  $\text{R}_1$  and  $\text{R}_2$  have the same meaning as in claim 1, wherein an *N,N*-disubstituted-4-amino-methylene-pyrazolone-(5) of the general formula given in claim 1 is hydrolysed at an elevated temperature in an acidic medium.  
 90

14. Process for the production of 4-formyl-pyrazolones-(5) according to claim 13, substantially as hereinbefore described and with reference to any of Examples 4—7.  
 95

15. 4-formyl-pyrazolones-(5) of the general formula given in claim 13, whenever prepared by the process according to claims 13 or 14.

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